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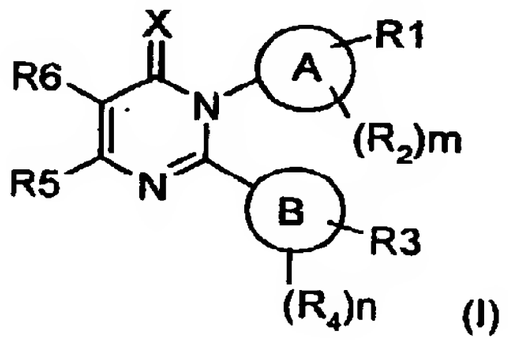
(54) Title: NOVEL PYRIMIDONE DERIVATIVES



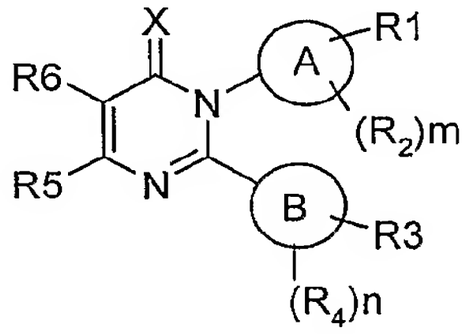
(I)

(57) Abstract: AbstractThe present invention relates to novel pyrimidone derivatives of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrimidone derivatives of the general formula (I).

NOVEL PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to novel pyrimidone derivatives of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrimidone derivatives of the general formula (I).



(I)

The present invention also provides a process for the preparation of the above said novel pyrimidone derivatives of the formula (I) pharmaceutically acceptable salts, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The novel pyrimidone derivatives of the present invention are useful for the treatment of inflammation and immunological diseases. Particularly the compounds of the present invention are useful for the treatment of inflammation and immunological diseases those mediated by cytokines such as TNF-α, IL-1, IL-6, IL-1β, IL-8 and cyclooxygenase such as COX-2 and COX-3. The compounds of the present invention are also useful for the treatment rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease; atherosclerosis; cancer; ischemic-induced cell damage; pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection; and diseases mediated by HIV-1; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-1, HSV-2) and herpes zoster viruses.

Background of Invention

It has been reported that Cyclooxygenase enzyme exists in three isoforms, namely, COX-1, COX-2 and COX-3. COX-1 enzyme is essential and primarily responsible for the regulation of gastric fluids whereas COX-2 enzyme is present at the basal levels and is reported to have a major role in the prostaglandin synthesis for inflammatory response. These prostaglandins are known to cause inflammation in the body. Hence, if the synthesis of these prostaglandins is stopped by way of inhibiting COX-2 enzyme, inflammation and its related disorders can be treated. COX-3 possesses glycosylation-dependent cyclooxygenase activity. Comparison of canine COX-3 activity with murine COX-1 and COX-2 demonstrated that this enzyme is selectively inhibited by analgesic/antipyretic drugs such as acetaminophen, phenacetin, antipyrine, and dipyrone, and is potently inhibited by some nonsteroidal antiinflammatory drugs. Thus, inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever. Recent reports show that inhibitors of COX-1 enzyme causes gastric ulcers, where as selective COX-2 and COX-3 enzyme inhibitors are devoid of this function and hence are found to be safe.

The present invention is concerned with treatment of immunological diseases or inflammation, notably such diseases are mediated by cytokines or cyclooxygenase. The principal elements of the immune system are macrophages or antigen-presenting cells, T cells and B cells. The role of other immune cells such as NK cells, basophils, mast cells and dendritic cells are known, but their role in primary immunologic disorders is uncertain. Macrophages are important mediators of both inflammation and providing the necessary "help" for T cell stimulation and proliferation. Most importantly macrophages make IL-1, IL-12 and TNF-α all of which are potent pro-inflammatory molecules and also provide help for T cells. In addition, activation of macrophages results in the induction of enzymes, such as cyclooxygenase-2 (COX-2) and cyclooxygenase-3 (COX-3), inducible nitric oxide synthase (iNOS) and production of free radicals capable of damaging normal cells. Many factors activate macrophages, including bacterial products, superantigens and interferon gamma (IFN γ). It is believed that phosphotyrosine kinases (PTKs) and other undefined cellular kinases are involved in the activation process.

Cytokines are molecules secreted by immune cells that are important in mediating immune responses. Cytokine production may lead to the secretion of other cytokines, altered cellular function, cell division or differentiation. Inflammation is the body's normal

response to injury or infection. However, in inflammatory diseases such as rheumatoid arthritis, pathologic inflammatory processes can lead to morbidity and mortality. The cytokine tumor necrosis factor-alpha (TNF-α) plays a central role in the inflammatory response and has been targeted as a point of intervention in inflammatory disease. TNF-α is a polypeptide hormone released by activated macrophages and other cells. At low concentrations, TNF-α participates in the protective inflammatory response by activating leukocytes and promoting their migration to extravascular sites of inflammation (Moser et al., J Clin Invest, 83, 444-55,1989). At higher concentrations, TNF-α can act as a potent pyrogen and induce the production of other pro-inflammatory cytokines (Haworth et al., Eur J Immunol, 21, 2575-79, 1991; Brennan *et al.*, Lancet, 2, 244-7, 1989). TNF-α also stimulates the synthesis of acute-phase proteins. In rheumatoid arthritis, a chronic and progressive inflammatory disease affecting about 1% of the adult U.S. population, TNF-α mediates the cytokine cascade that leads to joint damage and destruction (Arend *et al.*, Arthritis Rheum, 38, 151-60,1995). Inhibitors of TNF-α, including soluble TNF receptors (etanercept) (Goldenberg, Clin Ther, 21, 75-87, 1999) and anti-TNF-α antibody (infliximab) (Luong *et al.*, Ann Pharmacother, 34, 743-60, 2000), have recently been approved by the U.S. Food and Drug Administration (FDA) as agents for the treatment of rheumatoid arthritis.

Elevated levels of TNF-α have also been implicated in many other disorders and disease conditions, including cachexia, septic shock syndrome, osteoarthritis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis etc.

Elevated levels of TNF-α and/or IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF-α.

It can be seen that inhibitors of TNF-α are potentially useful in the treatment of a wide variety of diseases. Compounds that inhibit TNF-α have been described in several patents.

Excessive production of IL-6 is implicated in several disease states, it is highly desirable to develop compounds that inhibit IL-6 secretion. Compounds that inhibit IL-6 have been described in U.S. Pat. Nos. 6,004,813; 5,527,546 and 5,166,137.

The cytokine IL-1β also participates in the inflammatory response. It stimulates thymocyte proliferation, fibroblast growth factor activity, and the release of prostaglandin from synovial cells. Elevated or unregulated levels of the cytokine IL-1β have been associated with a number of inflammatory diseases and other disease states, including but not limited to adult respiratory distress syndrome, allergy, Alzheimer's disease etc. Since overproduction of IL-1β is associated with numerous disease conditions, it is desirable to develop compounds that inhibit the production or activity of IL-1β.

In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., Clinical Immunol Immunopathol. 55, 382, 1990). In studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than TNF-α. (Firestein, Am. J. Pathol. 140, 1309, 1992). At sites of local injection, neutrophil, lymphocyte, and monocyte emigration has been observed. The emigration is attributed to the induction of chemokines (e.g., IL-8), and the up-regulation of adhesion molecules (Dinarello, Eur. Cytokine Netw. 5, 517-531, 1994).

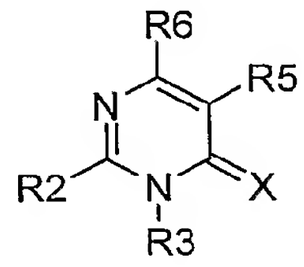
In rheumatoid arthritis, both IL-1 and TNF-α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice) intra-articular administration of TNF-α either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease (Brahn et al., Lymphokine Cytokine Res. 11, 253, 1992; and Cooper, Clin. Exp. Immunol. 898, 244, 1992).

IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil in filtration into sites of inlammation or injury (e.g., ischemia) is mediated chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowl disease, psoriasis, adult respiratory distress syndrome, cardiac and

renal reperfusion injury, thrombosis and glomerulonephritis. In addition to the chemotaxis effect on neutrophils, IL-8 has also has ability to activate neutrophils. Thus, reduction in IL-8 levels may lead to diminished neutrophil infiltration.

Few prior art reference which disclose the closest compounds are given here:

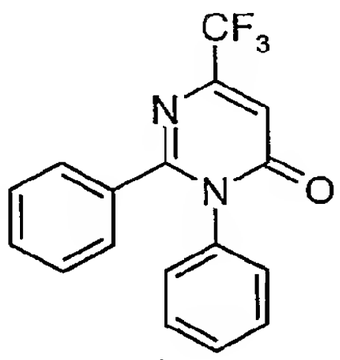
i) US patent Nos. 5,726,124 and 5,300,477 disclose novel herbicidal compounds of formula (IIa)



(IIa)

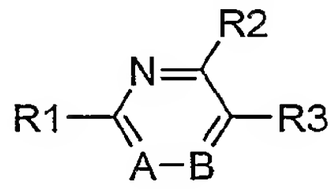
R_2 is a substituted or unsubstituted aryl group or a substituted or unsubstituted heteroaromatic group (e.g. a heteroaromatic ring structure having four to five carbon atoms and one heteroatom selected from the group consisting of nitrogen, sulfur and oxygen); R_3 is an alkyl, haloalkyl, polyhaloalkyl, haloalkenyl, polyhaloalkenyl, alkenyl, alkynyl, haloalkynyl, polyhaloalkynyl, alkoxyalkyl, dialkoxyalkyl, haloalkoxyalkyl, oxoalkyl, trimethylsilylalkynyl, cyanoalkyl or aryl group; R_5 is a hydrogen, halo, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxyalkyl, alkoxyimino, alkoxycarbonylalkyl, dialkoxyalkyl, formyl, haloalkyl, haloalkenyl, haloalkynyl, haloalkoxy, hydroxyalkyl, hydroxyimino, polyhaloalkyl, polyhaloalkenyl, polyhaloalkynyl, polyhaloalkoxy, trimethylsilylalkynyl, alkoxyalkoxy, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, cyanoalkyl, hydroxy or cyano group; and R_6 is a hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, haloalkyl, haloalkenyl, haloalkynyl, haloalkoxy, haloalkylthio, polyhaloalkyl, polyhaloalkenyl, polyhaloalkynyl, polyhaloalkoxy, polyhaloalkylthio, cycloalkyl, aryl, aryloxy, heterocyclyl, aralkyl, alkylamino, dialkylamino, dialkylaminocarbonyl, or cyano group; and X is oxygen or sulfur.

An example of these compounds is shown in formula (IIb)



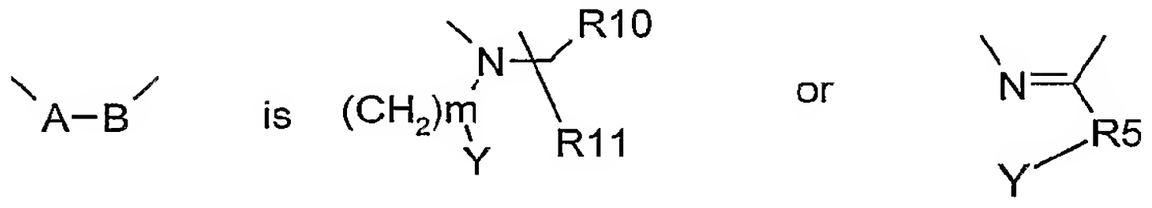
(IIb)

ii) US patent No. 5,474,996 discloses novel compounds of formula (IIc)



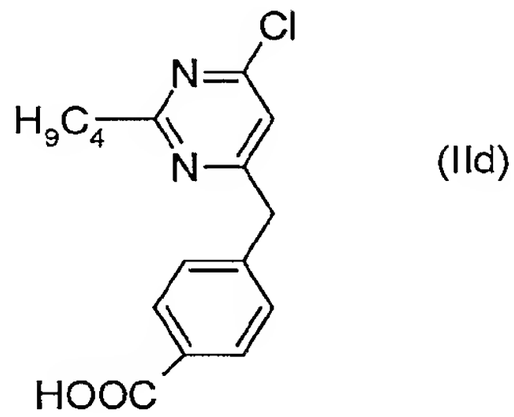
(IIc)

wherein



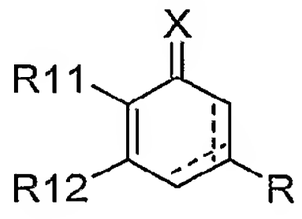
R_5 is a single bond or --$(CH_2)_m$ --, -NH-, etc., m is an integer of 0 to 4; Y is Y_1-B-Y_2 is a monocyclic aryl of 5 to 6 ring member or condensed ring of 8 to 10 ring members optionally containing at least one heteroatom chosen from oxygen, nitrogen and sulfur; R_{10} and R_{11} together form oxo group; R_2 is chosen from the group consisting of hydrogen, halogen, hydroxyl, mercapto, cyano, nitro, formyl, benzoyl, acyl of 1 to 6 carbon atoms, alkyl, alkenyl, alkoxy, alkylthio of up to 10 carbon atoms, phenyl, phenoxy, naphthyl, benzyl, phenylthio, biphenyl, biphenylmethyl and indole; R_3 is alkyl substituted with carboxy or esterified carboxy.

An example of these compounds is shown in formula (IId)



(IId)

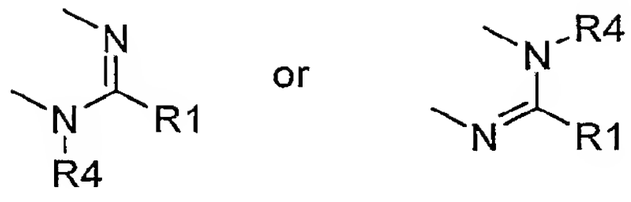
iii) US patent Nos. 6,420,385 and 6,410,729 discloses novel compounds of formula (IIe)



(IIe)

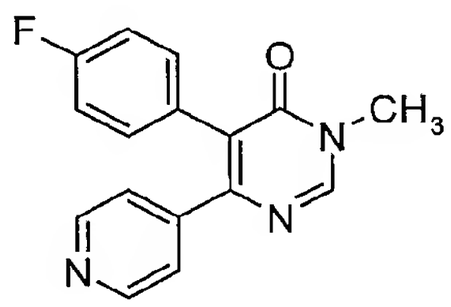
wherein

represents



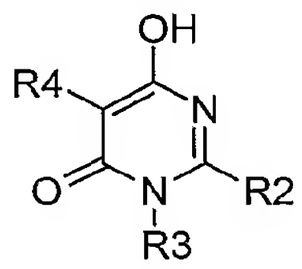
X is O, S or NR_5; R_1 and R_2 are each independently represent --Y or --Z--Y, and R_3 and R_4 are each independently --Z--Y or R_3 is a hydrogen radical; provided that R_4 is other than a substituted-aryl, (substituted-aryl)methyl or (substituted-aryl)ethyl radical; wherein each Z is independently optionally substituted alkyl, alkenyl, alkynyl, heterocyclyl, aryl or heteroaryl; Y is independently a hydrogen; halo, cyano, nitro, etc., R_5 is independently a hydrogen, optionally substituted alkyl, alkenyl, alkynyl etc., R_{11} and R_{12} each independently represent optionally substituted aryl or heteroaryl.

An example of these compounds is shown in formula (IIf)



(IIf)

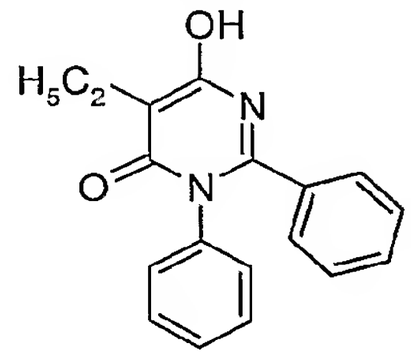
iv) US patent No. 4,771,040 discloses 6-oxopyrimidinyl(thiono)-phosphate pesticide compounds and intermediate of formula (IIg)



(IIg)

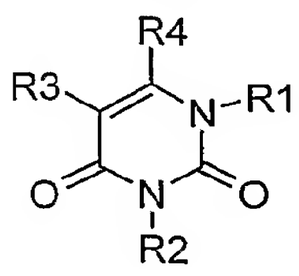
wherein R_2 represents hydrogen, optionally substituted alkyl, or alkoxy, alkylthio, dialkylamino or aryl; R_3 represents alkyl or aryl; R_4 represents hydrogen, halogen or alkyl.

An example of these compounds is shown in formula (IIh)



(IIh)

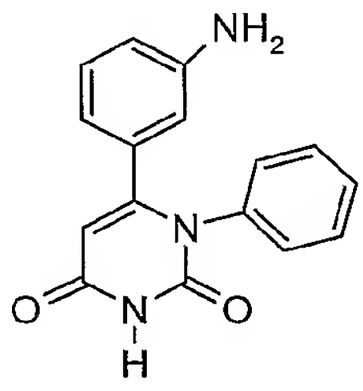
v) DE 2142317 discloses hypnotic uracil derivatives of formula (IIi)



(IIi)

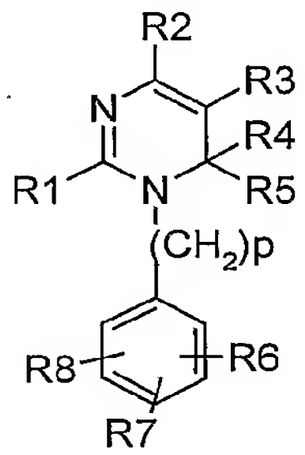
wherein R_1 is H, alkyl, alkenyl, dialkylaminoalkyl, or aralkyl; R_2 is H, alkyl, aryl, or halogen; R_3 is alkyl, alkenyl, cycloalkyl, aralkyl, aralkenyl, or aryl, R_4 is alkyl, alkenyl, cycloalkyl, aralkyl, aryl, etc.

An example of these compounds is shown in formula (IIj)



(IIj)

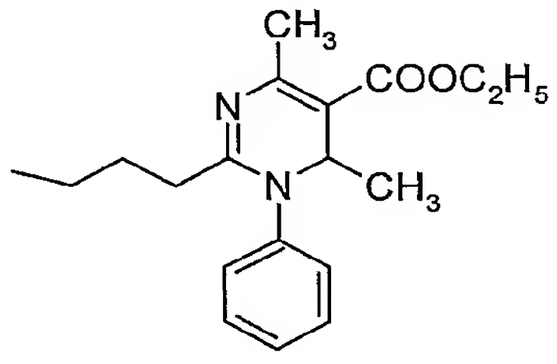
vi) US patent No. 5,470,975 discloses dihydropyrimidine derivatives of formula (IIk)



(IIk)

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, NR_4R_5 etc., R_2 is hydrogen, halogen, SR_4, etc., R_3 is R_4, --COOR, --$CONH_2$, CN, etc., R_4, R_5 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl etc., or R_4 and R_5 together with the carbon atoms to which they are attached form a carbonyl or a thiocarbonyl group; R_6 is --CN, alkyl, acyloxy, SO_2NH_2, aryl, furyl; R_7 is H, halogen, etc., R_8 is H, halogen, alkyl, alkoxy etc.,

An example of these compounds is shown in formula (III)



(III)

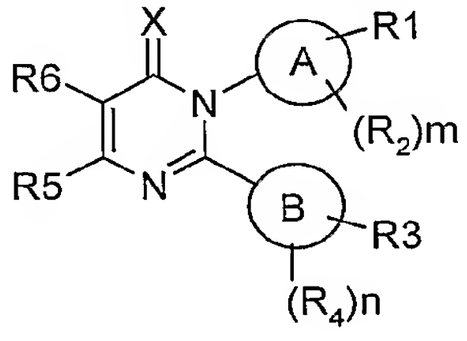
Objective of the Invention

We have focused our research to identify selective COX-2 and COX-3 inhibitors which are devoid of any side effects normally associated with anti-inflammatory agents. Our sustained efforts have resulted in novel pyrimidone derivatives of the formula (I). The

derivatives may be useful in the treatment of inflammation and immunological diseases. Particularly the compounds of the present invention are useful for the treatment of inflammation and immunological diseases those mediated by cytokines such as TNF-α, IL-1, IL-6, IL-1β, IL-8 and cyclooxygenase such as COX-2 and COX-3. The compounds of the present invention are also useful in the treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease; atherosclerosis; cancer; ischemic-induced cell damage; pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection; and diseases mediated by HIV-1; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-1, HSV-2) and herpes zoster viruses.

Summary of the Invention

The present invention relates to novel pyrimidone derivatives of the formula (I)



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein X represents oxygen, sulfur or NR, wherein R represents hydrogen, hydroxyl, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, alkoxyamino group; the rings represented by A and B are selected from aryl or heteroaryl; R^1 represents SR^7, or $S(O)_pR^8$; R^3 represents hydrogen, SR^7, or $S(O)_pR^8$, wherein R^7 represents alkyl or aryl; R^8 represents alkyl, amino or aryl group; and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylslfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; R^5 and R^6 may be

same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, aryl, aralkyl, haloalkyl, acyl, alkoxy, aryloxy, aralkoxy, heteroaryl, heterocyclyl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or COR^9, wherein R^9 represents hydroxyl, amino, halogen, alkoxy, aryloxy, monoalkylamino, dialkylamino, arylamino, groups; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2.

Detailed Description of the Invention

Suitable ring systems represented by A and B are selected from phenyl, naphthyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like.

Suitable groups represented by R^1 are selected from SR^7 or $S(O)_pR^8$. Suitable groups represented by R^3 are selected from hydrogen, SR^7, or $S(O)_pR^8$,

Suitable groups represented by R^2 and R^4 are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, iodine; hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, linear or branched (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; haloalkyl such as chloromethyl, chloroethyl, trifluoromethyl, trifluoroethyl, dichloromethyl, dichloroethyl and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like; alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like; alkoxyalkyl

group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like; carboxylic acid or its derivatives such as esters, amides and acid halides.

Suitable groups represented by R^5 and R^6 are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, iodine; hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, linear or branched (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; haloalkyl such as wherein the alkyl is as defined above; aryl such as phenyl, naphthyl and the like; aralkyl such as benzyl, phenylethyl, phenylpropyl and the like; aryloxy group such as phenoxy, napthoxy and the like; aralkoxy group such as phenylmethoxy, phenylethoxy, phenylpropoxy, and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like; heterocyclyl group such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like; alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like or COR^9, wherein R^9 represents hydroxyl, amino, halogen, alkoxy, aryloxy, monoalkylamino, dialkylamino, arylamino, groups.

Suitable groups represented by R^9 are selected from hydroxyl, amino, halogen, linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like, which may be substituted; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; aryloxy group such as phenoxy, napthoxy and the like; arylamino such as phenyl amino, naphthyl amino and the like.

The groups represented by R^5 and R^6 may be substituted by the substituents selected from halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, aryl, aralkyl, haloalkyl, acyl, alkoxy, aryloxy, aralkoxy, heteroaryl, heterocyclyl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives. The substituents are as defined above.

Suitable groups represented by R^7 are selected from linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl.

Suitable groups represented by R^8 are selected from amino, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl.

Suitable groups represented by R are selected from hydrogen, hydroxyl, amino, hydroxylamino, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; aryl group such as phenyl, naphthyl and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; aryl group such as phenyl or naphthyl; alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like; arylamino such as phenyl amino, naphthyl amino and the like; alkoxyamino such as methoxyamino, ethoxyamino, propoxy amino and the like.

m and n are integers ranging from 0-2.

Pharmaceutically acceptable salts of the present invention include alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, guanidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine etc. Salts may include sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates,

glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Representative compounds according to the present invention include:

5-Cyano-4-methylthio-1-(4-methylthio-phenyl)-2-phenyl-1,6-dihydro-pyrimidin-6-one;

5-Cyano-4-methylthio-1-(4-methylthio-phenyl)-2-(4-trifluoromethylphenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-fluorophenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-2-(4-methylsulfonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-fluorophenyl)-2-(4-methylsulfonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylsulfonyl-2-(4-methylsulfonyl-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylsulfonyl-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylthio-2-(4-sulfamoyl-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-fluorophenyl)-1-(4-methylthio-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-fluorophenyl)-1-(4-methylsulfonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-fluorophenyl)-4-methylthio-1-(4-sulfamoyl-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

2-(4-Methanesulfonyl-phenyl)-4-methylsulfanyl-6-oxo-1-(4-methylphenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid;

2-(4-Methanesulfanyl-phenyl)-4-methylsulfanyl-6-oxo-1-(4-methylphenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid;

2-(4-Fluroro-phenyl)-4-methylsulfanyl-6-oxo-1-(4-methylphenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid;

5-Carboxy-4-methylthio-1-(4-methylthio-phenyl)-2-phenyl-1,6-dihydro-pyrimidin-6-one;

5-Carbamoyl-2-(4-fluorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Chloro-2-(4-chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

2-(4-Chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

2-(4-Chlorophenyl)-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

1-(4-Methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

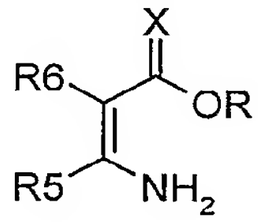
1-(4-Methylphenyl)-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

4-(5-Cyano-4-methylthio-6-oxo-2-phenyl-6H-pyrimidin-1-yl)-benzenesulfonamide;

4-(5-Cyano-4-methylthio-6-oxo-2-(4-methylphenyl)-6H-pyrimidin-1-yl)-benzenesulfonamide and

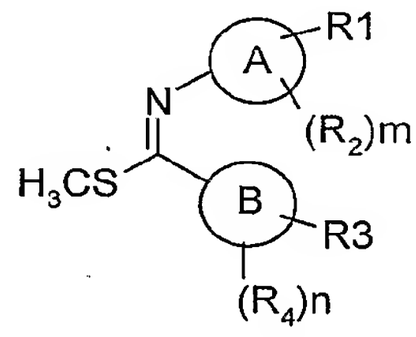
4-(5-Carboxy-4-methylthio-6-oxo-2-phenyl-6H-pyrimidin-1-yl)-benzenesulfonamide.

According to another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the formula (I) wherein all symbols are as defined earlier, which comprises reacting a compound of the formula (Ia)



(Ia)

where R represent (C_1-C_3) alkyl group, X, R^5 and R^6 are as defined above, with a compound of the formula (Ib)



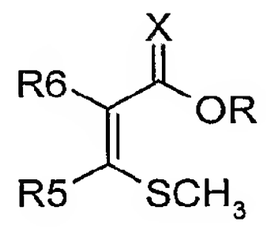
(Ib)

wherein all symbols are as defined above, to produce a compound of formula (I).

The reaction of compound of formula (Ia) with compound of formula (Ib) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, pyridine, ethanol, methanol,

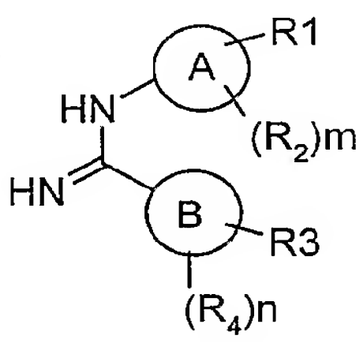
isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like or by neat reactions. The condensation reaction may be carried out under acidic conditions using mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction may be carried out by using phase transfer catalysts viz. triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylylmethylammonium chloride (aliquat 336) and the like. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization. The reaction may be carried out for period in the range of 2 to 20 h.

According to another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the formula (I) wherein all symbols are as defined earlier, which comprises reacting a compound of the formula (Ic)



(Ic)

where R represent (C_1-C_3) alkyl group and all other symbols are as defined above, with a compound of the formula (Id)



(Id)

wherein all symbols are as defined above, to produce a compound of formula (I).

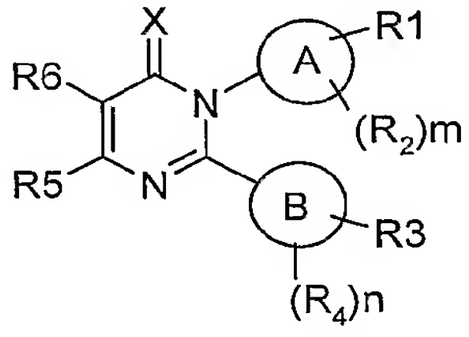
The reaction of compound of formula (Ic) with compound of formula (Id) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, pyridine, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid etc, a mixture thereof or the like or by neat reactions. The condensation reaction may be carried out under acidic conditions using mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction may be carried out by using phase transfer catalysts viz.

triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylylmethylammonium chloride (aliquat 336) and the like. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization. The reaction may be carried out for period in the range of 30 min. to 10 hours.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel pyrimidone derivatives of the formula (I) wherein any of the groups R^1 or R^3 represent SR^7, wherein R^7 represents alkyl or aryl to novel pyrimidone derivatives of the formula (I) wherein any of the groups R^1 or R^3 represent $S(O)_pR^8$, where p represents 1 or 2 and R^8 represents alkyl or aryl; by using suitable oxidizing agent. The oxidizing agent may be selected from potassium peroxymonosulfate (Oxone), hydrogen peroxide, tert-butylperoxide, Jones reagent, peracid [e.g peracetic acid, perbenzoic acid, m-chloroperbenzoic acid etc], chromic acid, potassium permanganate, alkali metal periodate [e.g sodium periodate, etc], magnesium mono peroxypthalate, osmium tetroxide/N-methylmorpholine-N-oxide, sodium tungstate, and the like. The oxidation is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [eg. methanol, ethanol, etc.], a mixture thereof or the like. The reaction temperature is usually carried out under cooling to refluxing conditions.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel pyrimidone derivatives of the formula (I) wherein R^1 or R^3 represent $S(O)_pR^8$, where p is 1 or 2, R^8 represents alkyl or aryl may be converted to novel pyrimidone derivatives of the formula (I) wherein R^1 or R^3 represent $S(O)_pR^8$, where p is 1 or 2, R^8 represents amino by using the procedure described in the literature (Huang *et.al.* Tetrahedron Lett., 39, 7201, 1994).

In yet another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the formula (I) wherein either of R^1 or R^3 represent $S(O)_pR^8$, wherein R^8 represents amino group and p represents an integer of 1 or 2 and all other symbols are as defined earlier, which comprises reacting compound of formula (Ie) wherein all symbols are as defined earlier

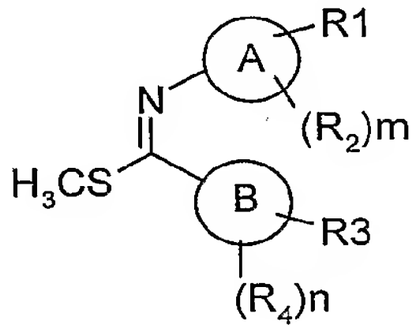


(Ie)

where R^1 represents hydrogen with chlorosulfonic acid and ammonia.

The reaction of compound of formula (Ie) with chlorosulfonic acid and ammonia may be carried out in the presence of solvents such as acetic acid, dichloromethane, acetone, tetrahydrofuran, dioxane, ethyl acetate, chloroform, water, an alcohol and the like or a mixture thereof. The reaction may be carried out at a temperature in the range of 50 °C to reflux temperature for period in the range of 2 to 12 h.

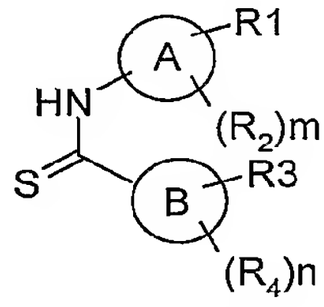
In yet another embodiment of the present invention, there is provided a novel intermediate of formula (Ib)



(Ib)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein the rings represented by A and B are selected from aryl or heteroaryl; R^1 and R^3 are different and represent hydrogen, SR^7, wherein R^7 represents alkyl or aryl, or $S(O)_pR^8$, wherein R^8 represents alkyl, amino or aryl group and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2.

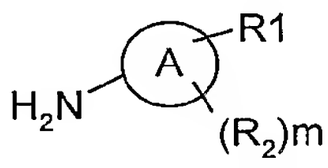
In yet another embodiment of the present invention, there is provided a process for the preparation of novel intermediate of formula (Ib), which comprises, methylating the compound of formula (Ib-2)



(Ib-2)

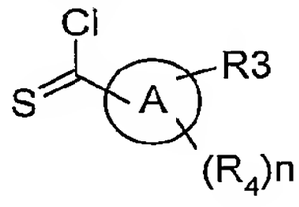
The methylation of Ib-2 may be carried out by treating with methylating agent like methyliodide, dimethylsulphate and diazomethane etc., in the presence of base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, tetrahydrofuran, methanol, t-butanol, dioxane, isopropanol, ethanol, water etc.

In yet another embodiment of the present invention, there is provided a process for the preparation of novel intermediate of formula (Ib-2), which comprises, reacting compound of formula (Ib-3)



(Ib-3)

where R_1 and R_2 all are as defined above with compound of formula (Ib-4)

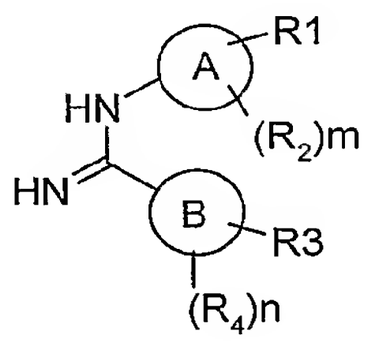


(Ib-4)

where all symbols are as defined above.

The reaction of compound of formula (Ib-3) with compound of formula (Ib-4) may be carried out in solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, pyridine, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid etc, a mixture thereof or the like or by neat reactions. The reaction may be carried out at a temperature in the range of 0 to 200 °C for period in the range of 30 min. to 5 hours.

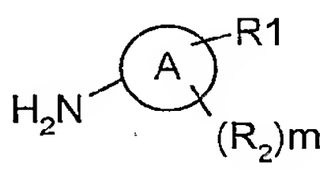
In yet another embodiment of the present invention, there is provided a novel intermediate of formula (Id)



(Id)

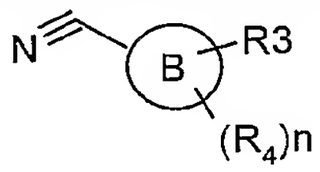
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein the rings represented by A and B are selected from aryl or heteroaryl; R^1 and R^3 are different and represent hydrogen, SR^7, wherein R^7 represents alkyl or aryl, or $S(O)_pR^8$, wherein R^8 represents alkyl, amino or aryl group and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2.

In yet another embodiment of the present invention, there is provided a process for the preparation of novel intermediate of formula (Id), which comprises, reacting compound of formula (Ib-3)



(Ib-3)

where R_1 and R_2 all are as defined above with compound of formula (Id-1)



(Id-1)

where all symbols are as defined above.

The reaction of compound of formula (Ib-3) with compound of formula (Id-1) may be carried out in the presence of catalysts like aluminium chloride, triethyl aluminium, sodium hydride, sodium methoxide, butyl lithium, lithium diisopropylamine, sodium bis trimethyl silylamide, lithium bis trimethyl silylamide, using solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like or by neat reactions. The reaction may be carried out at a temperature in the range of 50 to 200 °C for period in the range of 30 min. to 10 hours.

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above-mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, tetrahydrofuran, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline, guanidine and the like, ammonium or substituted ammonium salts, aluminum salts. Amino acid such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine etc may be used for the preparation of amino acid salts. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and in solvents like ethyl acetate, ether, alcohols, acetone, tetrahydrofuran, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Pharmaceutically acceptable solvates of the compounds of formula (I) forming part of this invention may be prepared by conventional methods such as dissolving the compounds of formula (I) in solvents such as water, methanol, ethanol, mixture of solvents such as acetone:water, dioxane:water, N,N-dimethylformamide:water and the like, preferably water and recrystallizing by using different crystallization techniques.

The present invention provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable hydrates and solvates in combination with the usual pharmaceutically employed

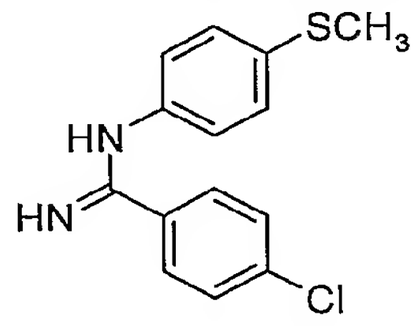
carriers, diluents and the like, useful for the treatment of inflammation, arthritis, pain, fever, psoriasis, allergic diseases, asthma, inflammatory bowel syndrome, gastro-intestinal ulcers, cardiovascular disorders including ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, particularly brain damage caused by stroke, other pathological disorders associated with free radicals.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, aerosols, suspensions and the like, may contain flavoring agents, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The present invention is provided by the examples given below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

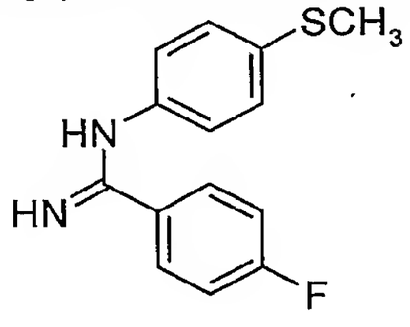
Preparation 1

Synthesis of N-(4-methylthio-phenyl)-4-chlorobenzamidine



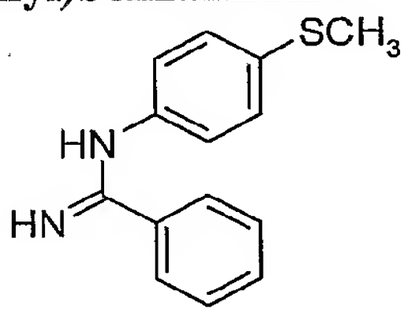
Finely powdered anhydrous aluminium chloride (0.83g, 6mmol) was added to a stirred mixture of 4-chlorobenzonitrile (0.6875g, 5mmol) and 4-methylthioaniline (0.695g, 5mmol) over a period of 30 min. The reaction mixture was heated at 180 -190 °C for 3 hours with stirring and allowed to cool to 50 °C. The resultant mixture was triturated with ethyl acetate and basified with sodium hydroxide (20%) solution. The ethyl acetate layer was washed with water, dried over anhydrous sodium sulphate and concentrated to give the crude product, which was purified by column chromatography to yield the title compound (0.6g, 43.4%, purity 98.8% by HPLC), mp 148 – 150 °C. ^{1}H-NMR ($CDCl_3$): δ 2.48 (s, 3H), 6.90-6.97(m, 2H), 7.11-7.41(m, 4H), 7.74 (bs, 2H). MS m/z: 277.0 (M^+)

Preparation 2
Synthesis of N-(4-methylthio-phenyl)-4-fluorobenzamidine



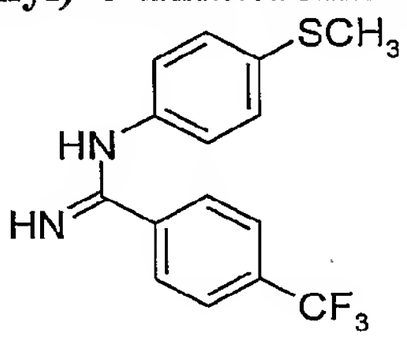
The title compound was prepared from 4-fluorobenzonitrile (2.176g, 17.98mmol) and 4-methylthioaniline (2.5g, 17.98mmol) by following the procedure described in preparation 1, (2.06g, 44.1%, purity 98.8% by HPLC), mp121 - 124 °C. ^{1}H-NMR ($CDCl_3$): δ 2.48 (s, 3H), 4.82 (bs, 2H, D_2O exchangeable), 6.91-6.93 (d, 2H), 7.1-7.14 (m, 2H), 7.26-7.30 (m, 2H), 7.86 (bs, 2H). MS m/z: 261.1(M^+)

Preparation 3
Synthesis of N-(4-methylthio-phenyl)benzamidine



The title compound was prepared from benzonitrile (3.705g, 35.97mmol) and 4-methylthioaniline (5.0g, 35.97mmol) by following the procedure described in preparation 1, (3.66g, 42.1%, purity 99.8% by HPLC), mp 129 – 131 °C. ^{1}H-NMR ($CDCl_3$): δ 2.49 (s, 3H), 4.84 (bs, 2H), 6.94-6.96 (d, 2H), 7.26-7.31 (m, 2H), 7.45-7.49 (m, 3H), 7.87-7.88 (d, 2H). MS m/z: 243.2 (M^+)

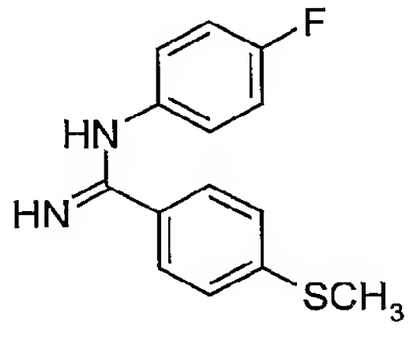
Preparation 4
Synthesis of N-(4-methylthio-phenyl)-4-trifluoromethylbenzamidine



The title compound was prepared from 4-trifluoromethylbenzonitrile (0.62g, 3.6mmol) and 4-methylthioaniline (0.5g, 3.6mmol) by following the procedure described in preparation 1, (0.495g, 44.4%, purity 98.3% by HPLC), mp 144 – 146 °C. ^{1}H-NMR ($CDCl_3$): δ 2.49 (s, 3H), 4.8 (bs, 2H), 6.93-6.95 (d, 2H), 7.26-7.32 (m, 2H), 7.70-7.72 (d, 2H), 7.99-8.01 (d, 2H). MS m/z: 311.1(M^+).

Preparation 5

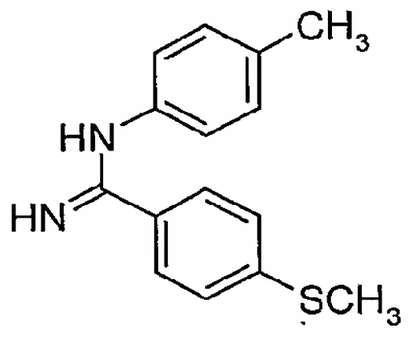
Synthesis of N-(4-fluorophenyl)-4-methylthiobenzamidine



The title compound was prepared from 4-methylthiobenzonitrile (0.50g, 33.6mmol) and 4-fluoroaniline (0.372g, 33.6mmol) by following the procedure described in preparation 1, (0.43g, 49.3%, mp 145 – 147 °C, purity 94.7% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 2.52 (s, 3H), 6.93-6.94 (m, 3H), 7.17-7.32 (m, 5H). MS m/z: 261.1(M^+)

Preparation 6

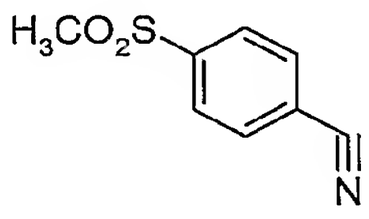
Synthesis of N-(4-methylphenyl)-4-methylthiobenzamidine



The title compound was prepared from 4-methylthiobenzonitrile (2.50g, 16.78mmol) and 4-methylaniline (1.789g, 16.78mmol) by following the procedure described in preparation 1, (2.05g, 47.6%, purity 79% by HPLC), mp 143 – 145 °C. ^{1}H-NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.52 (s, 3H), 4.75 (bs, 2H, D_2O exchangeable), 6.87 – 6.89 (d, 2H), 7.14 -7.16 (d, 2H), 7.27 – 7.29 (d, 2H), 7.7 – 7.79 (d, 2H). MS m/z: 257.1(M^+).

Preparation 7

Synthesis of 4-methylsulphonylbenzonitrile

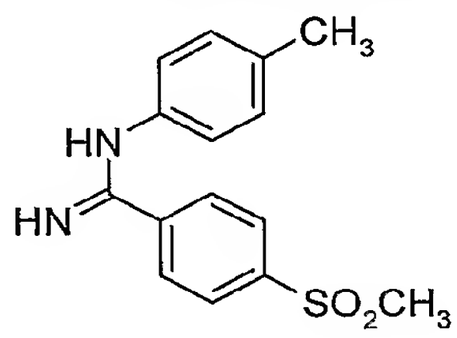


A solution of oxone (18.42g, 0.03mol) in water (70ml) was added dropwise to the vigorous stirred solution of 4-methylthiobenzonitrile (1.49g, 0.01mol) in methanol (50ml) at 20 °C and stirring was continued for three hours. The reaction mixture was diluted with water (50ml) and extracted with ethyl acetate. The ethyl acetate extract was washed with water,

dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound (1.3g, 72.2%), mp 145 – 149 °C. The compound was used with out any purification for the next step. ^{1}H-NMR ($CDCl_3$): δ 3.1 (s, 3H), 7.8 – 7.9 (d, 2H), 8.08 – 8.1 (d, 2H).

Preparation 8

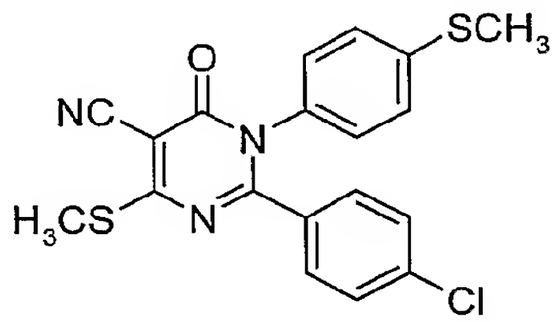
Synthesis of N-(4-methylphenyl)-4-methylsulphonylbenzamidine



The title compound was obtained from 4-methylsulphonylbenzonitrile (2.00g, 11mmol) (obtained according to the procedure described in preparation 7) and 4-methylaniline (1.18g, 11mmol) according to the procedure described in preparation 1, (1.25g, 39.3%, purity 90.7% by HPLC), mp 187 – 189 °C. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H), 3.07(s, 3H), 4.92 (bs, 2H, D_2O exchangeable), 6.87 – 6.89 (d, 2H), 7.18-7.20 (d, 2H), 8.01- 8.03 (d, 2H), 8.08 – 8.1 (d, 2H). MS m/z: 289.1(M^+).

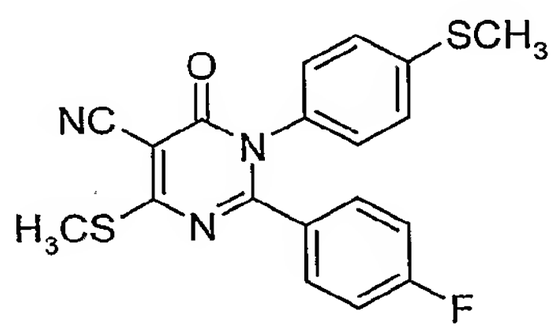
Example 1

Synthesis of 5-cyano-2-(4-chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one



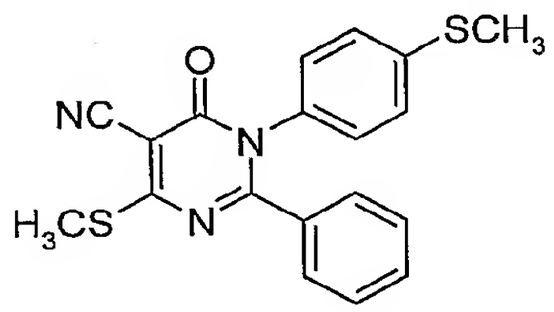
A mixture of ethyl 2-cyano-3,3-dimethylthioacrylate (1.345g, 6.2mmol) and N-(4-methylthio-phenyl)-4-chlorobenzamidine (1.7g, 6.2mmol) (obtained according to the procedure described in preparation 1) was heated at 110 -120 °C for 2 hours. The gummy mass thus obtained was purified by column chromatography to give the title compound (1.1g, yield 44.4%, purity 94.6% by HPLC), mp 206-207 °C.^{1}H-NMR ($CDCl_3$): δ 2.47 (s, 3H), 2.66 (s, 3H), 6.99 –7.01 (d, 2H), 7.18-7.30 (m, 6H). IR (KBr) cm^{-1}: 2218(-CN), 1672 (-C=O). MS m/z: 400.1(M^+).

Example 2
Synthesis of 5-cyano-2-(4-fluorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one



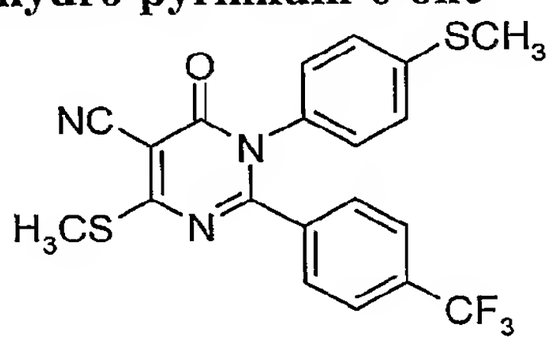
The title compound was prepared from ethyl 2-cyano-3,3-dimethylthioacrylate (1.25g, 5.76mmol) and N-(4-methylthio-phenyl)-4-fluorobenzamidine (1.50g, 5.76mmol) (obtained in preparation 2) according to the procedure described in example 1, (1.8g, 81.8%, purity 99.4% by HPLC), mp 204-207 °C. ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H), 2.67 (s, 3H), 6.94 –7.01 (m, 4H), 7.17-7.26 (m, 2H), 7.35-7.38 (m, 2H). IR (KBr) cm^{-1}: 2218(-CN), 1678 (-C=O). MS m/z: 384 (M^+)

Example 3
Synthesis of 5-cyano-4-methylthio-1-(4-methylthio-phenyl)-2-phenyl-1,6-dihydro-pyrimidin-6-one



The title compound was prepared from ethyl 2-cyano-3,3-dimethylthioacrylate (1.345g, 6.2mmol) and N-(4-methylthio-phenyl)benzamidine (1.50g, 6.2mmol) (obtained in preparation 3) by following the procedure described in example 1, (1.28g, yield 56.6%, purity 98.8% by HPLC), mp 204 – 205 °C. ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.67 (s, 3H), 6.99 – 7.01 (m, 2H), 7.15 -7.17 (m, 2H), 7.26 - 7.37 (m, 5H). IR (KBr) cm^{-1}: 2218 (-CN), 1682 (-C=O). MS m/z: 366 (M^+).

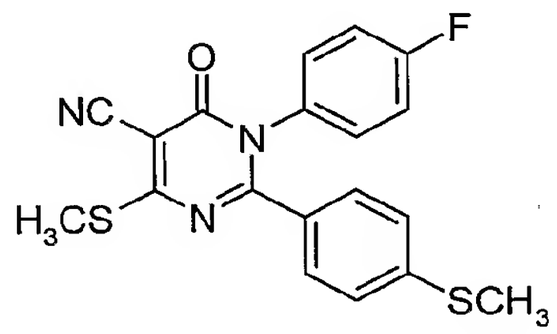
Example 4
Synthesis of 5-cyano-4-methylthio-1-(4-methylthio-phenyl)-2-(4-trifluoromethylphenyl)-1,6-dihydro-pyrimidin-6-one



The title compound was prepared from ethyl 2-cyano-3,3-dimethylthioacrylate (1.0g, 4.6mmol) and the N-(4-methylthio-phenyl)-4-trifluoromethylbenzamidine (1.50g, 4.8mmol) (obtained according to the procedure described in preparation 4) by following the procedure described in example 1, (1.6g, 80.1%, purity 99.3% by HPLC), mp 228 – 229 °C. ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H), 2.66 (s, 3H), 6.99 – 7.01 (d, 2H), 7.17-7.19 (d, 2H), 7.46 - 7.48 (d, 2H), 7.54 - 7.56 (d, 2H). IR (KBr) cm^{-1}: 2215 (-CN), 1680 (-C=O). MS m/z: 434.2 (M^+).

Example 5

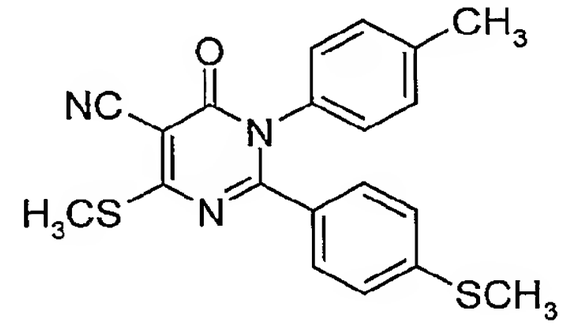
Synthesis of 5-cyano-1-(4-fluorophenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one



The title compound was prepared from ethyl 2-cyano-3,3-dimethylthioacrylate (0.334g, 1.54mmol) and N-(4-fluorophenyl)-4-methylthiobenzamidine (0.40g, 1.54mmol) (obtained in preparation 5) by following the procedure described in example 1, (0.32g, 54.3%, purity 99.2% by HPLC), mp 219 – 221 °C. ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H), 2.68 (s, 3H), 7.05 – 7.12 (m, 6H), 7.23 -7.27 (m, 2H). IR (KBr) cm^{-1}: 2218 (-CN), 1667 (-C=O). MS m/z: 384 (M^+).

Example 6

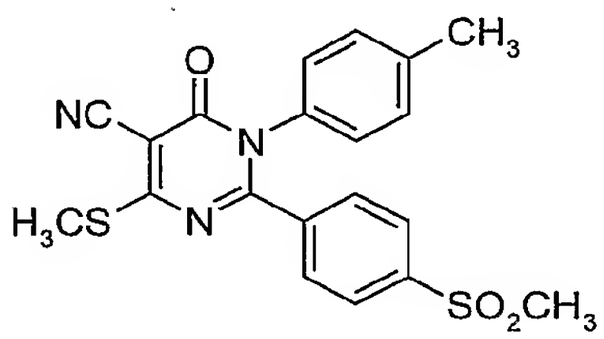
Synthesis of 5-cyano-1-(4-methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one



The title compound was prepared from ethyl 2-cyano-3,3-dimethylthioacrylate (0.848g, 3.9mmol) and N-(4-methylphenyl)-4-methylthiobenzamidine (1.0g, 3.9mmol) (obtained in preparation 6) by following the procedure described in example 1, (0.68g, 46%, purity 99.3% by HPLC), mp 196 - 198 °C. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.45 (s, 3H), 2.67 (s, 3H), 6.99 – 7.01 (m, 2H), 7.04 - 7.06 (m, 2H), 7.14 – 7.18 (m, 2H), 7.26-7.28 (m, 2H). IR (KBr) cm^{-1}: 2215 (-CN), 1688 (-C=O). MS m/z: 380.4 (M^+).

Example 7

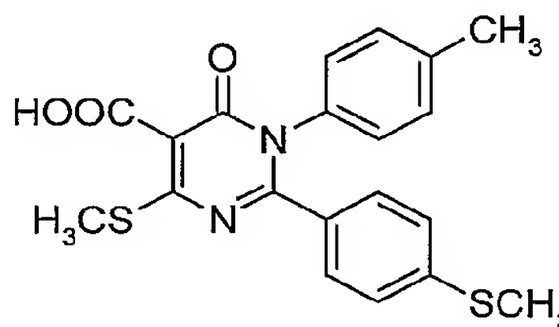
Synthesis of 5-cyano-1-(4-methylphenyl)-2-(4-methylsulphonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one



The title compound was prepared from ethyl 2-cyano-3,3-dimethylthioacrylate (0.378g, 1.74mmol) and N-(4-methylphenyl)-4-methylsulphonylbenzamidine (0.5g, 1.74mmol) (obtained in preparation 8) according to the procedure described in example 1, (0.43g, 59.6%, purity 99.1% by HPLC), mp 242 - 244 °C. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.65 (s, 3H), 3.04 (s, 3H), 6.95 – 6.97 (d, 2H), 7.15 - 7.17 (d, 2H), 7.51 – 7.54 (d, 2H), 7.82 - 7.84 (d, 2H). IR (KBr) cm^{-1}: 2217 (-CN), 1696 (-C=O). MS m/z: 412 (M^+).

Example 8

Synthesis of 5-carboxy-1-(4-methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one



A mixture of 5-cyano-1-(4-methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one (2.5g, 6.59mmol) (obtained according to the procedure described in example 6) and potassium hydroxide (40%, 25ml) solution was refluxed for 2 hours. The reaction mixture was poured onto ice-water, neutralised with dilute hydrochloric acid and filtered. The solid thus obtained was washed with water and dried to yield title compound (2.12g, 80.8%, purity 91.6% by HPLC), mp 173 - 175 °C. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.53 (s, 3H), 2.69 (s, 3H), 7.16 – 7.18 (d, 2H), 7.26 - 7.37 (m, 4H), 7.92 – 7.94 (d, 2H), 14.0 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3311(-COOH), 1702(-C=O). MS m/z: 398.5 (M^+).

Described below are the examples of pharmacological assays used for finding out the efficacy of the compounds of the present invention wherein their protocols and results are provided.

Rat Carrageenan Paw Edema Test

The carrageenan paw edema test was performed as described by Winter et al (Proc.Soc. Exp Biol Me., 111, 544, 1962). Male Wistar rats were selected and the body weight were equivalent within each group. The rats were fasted for eighteen hours with free access to water. The rats were dosed orally with the test compound suspended in vehicle containing 0.5% methylcellulose. The control rats were administered the vehicle alone. After one hour the rats were injected with 0.1 ml of 1% Carrageenan solution in 0.9% saline into the sub plantar surface of the right hind paw. Paw thickness was measured using vernier calipers at 0 time, after 2 and 3 hours. The average of foot swelling in drug treated animals was compared with that of control animals. Anti-inflammatory activity was expressed as the percentage inhibition of edema compared with control group [Arzneim-Forsch/Drug Res 43(I), 1, 44-50,1993; Otterness and Bliven, Laboratory Models for Testing NSAIDs, In Non-Steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed.1985)]. The data of the selected compounds in this invention are summarized in Table I. In order to evaluate their role on the ulcer formation, the animals were sacrificed by cervical dislocation, the stomach removed and flushed with 1% formalin (10ml). The stomach was opened along the greater curvature. The haemorrhagic puncta and sulci were identified macroscopically. The presence or absence of stomach lesions was scored. The incidence of ulceration was calculated from the number of rats that showed atleast one gastric ulcer or haemorrhagic erosion.

Table I

Example No.	Rat Paw Edema model % Inhibition (10mg/kg body weight)	Gastro-ulcerogenic potential (% incidence of ulceration)
1	10	29
2	10	39
4	10	38.5
6	10	40.2

***In vitro* evaluation of Cycloxygenase-2 (COX-2) inhibition activity**

The compounds of this invention exhibited *in vitro* inhibition of COX-2. The COX-2 inhibition activity of the compounds illustrated in the examples was determined by the following method.

Human Whole Blood Assay

Human whole blood provides a protein and cell rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors.

human blood with lipopolysaccharide (LPS), which induces COX-2 production in the blood.

Method

Fresh blood was collected in tubes containing potassium EDTA by vein puncture from male volunteers. The subjects should have no apparent inflammatory conditions and not taken NSAIDs for atleast 7 days prior to blood collection. Blood was treated with aspirin *in vitro* (10μg/ml, at time zero) to inactivate COX-1, and then with LPS (10μg/ml) along with test agents or vehicle. The blood was incubated for 24 h at 37 °C, after which the tubes were centrifuged, the plasma was separated and stored at -80 °C (J Pharmacol Exp Ther 271, 1705, 1994; Proc Natl Acad Sci USA 96, 7563, 1999). The plasma was assayed for PGE2 using Cayman ELISA kit as per the procedure outlined by the manufacturer (Cayman Chemicals, Ann Arbor, USA). The plasma was also tested for TNF-α, IL-1β, and IL-6 using appropriate human ELISA kit as per the procedure of manufacturer (Cayman Chemicals, Ann Arbor, USA). Representative results of COX-2 inhibition are shown in Table II.

Table II

Example No.	Conc. (μM)	COX-2 % Inhibition
2	1	53.38
4	10	50.07
5	1	40.55
6	1	55.71

Tumor Necrosis Factor Alpha (TNF-α)

This assay determines the effect of test compounds on the production of TNF-α from human monocytes. Compounds were tested for their ability to downregulate the production of TNF-α in activated monocytes. Test compounds were incubated for three, six and twenty four hours with human monocytes. Lipopolysaccharide was used to stimulate the monocytes. The level of TNF-α was quantitated using Enzyme-Linked Immunosorbent assay performed in a 96 well format. Representative results of TNF-α inhibition are shown in Table III.

Table III

Example No.	Conc. (μM)	TNF-α % Inhibition
6	1	28.83

Interleukin-6(IL-6)

This assay determines the effect of test compounds on the production of IL-6 from human monocytes. Compounds are tested for their ability to downregulate the production of IL-6 in activated monocytes. Test compounds were incubated for three, six and twenty four hours with human monocytes. Lipopolysaccharide was used to stimulate the monocytes. The level of Interleukin-6 is quantitated using Enzyme-Linked Immunosorbent assay performed in a 96 well format. Representative results of IL-6 inhibition are shown in Table IV.

Table IV

Example No.	Conc. (μM)	IL-6 % Inhibition
2	0.25	44.96
4	0.25	48.36
5	0.25	51.05
6	0.25	41.37

Inhibitory Action on Adjuvant Arthritis

Compounds were assayed for their activity on rat adjuvant induced arthritis according to Theisen-Popp et al., (Agents Actions 42, 50-55,1994). Six - seven weeks old, Wistar rats were weighed, marked and assigned to groups [a negative control group in which arthritis was not induced (non-adjuvant control), a vehicle-treated arthritis control group, test substance treated arthritis group]. Adjuvant induced arthritis was induced by an injection of *Mycobacterium butyricum* (Difco) suspended in liquid paraffin into the sub-plantar region of the right hind paw (J Pharmacol Exp Ther, 284, 714, 1998). Body weight, contra-lateral paw volumes were determined at various days (0, 4, 14, 21) for all the groups. The test compound or vehicle was administered orally beginning post injection of adjuvant and continued for 21 days. On day 21, body weight and paw volume of both right and left hind paw, spleen, and thymus weights were determined. In addition, the radiograph of both hind paws was taken to assess the tibio-tarsal joint integrity. Hind limb below the stifle joint was removed and fixed in 1% formalin saline. At the end of the experiment, plasma samples were analysed for cytokines, interleukins and prostaglandins. The presence or absence of lesions in the stomachs was also observed.

Two-factor (`treatment` and `time`) Analysis of Variance with repeated measures on `time` were applied to the % changes for body weight and foot volumes. A post hoc Dunnett's test

was conducted to compare the effect of treatments to vehicle. A one-way Analysis of Variance was applied to the thymus and spleen weights followed by the Dunnett's test to compare the effect of treatments to vehicle. Dose-response curves for % inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a nonlinear Least Squares' regression. ID_{50} was defined as the dose corresponding to a 50% reduction from the vehicle and was derived by interpolation from the fitted 4-parameter equation

In-vitro Anti-Cancer activity

The compounds of the present invention were also tested for anticancer activity. Each test compound was screened against a battery of 60 human cell lines obtained from eight organs. The cell suspensions were diluted according to the particular cell type and the target cell density (5000-40,000 cells per well based on cell growth characteristics) was added into 96-well micro titer plates. Inoculates were allowed a pre-incubation period of 24 h at 37 °C for stabilization. Dilutions at twice the intended test concentrations were added at time zero in 100 µl aliquots to micro titer plate wells. Usually test compounds were evaluated at five 10-fold dilutions. The highest well concentration used in the test is 10^{-4} M. The cells were then incubated in the presence of the test compound for further 48 h in 5% CO_2 atmosphere and 100% humidity. After completion of the incubation period the adherent cells were fixed to the plate by means of trichloroacetic acid. After three to five times washing, the cell layer was treated with the protein stain Sulforhodamine B. The optical density, which is proportional to protein mass, was then read by spectrophotometric plate readers at a wavelength of 515 nm. The anticancer activity is shown in figures 1-4.

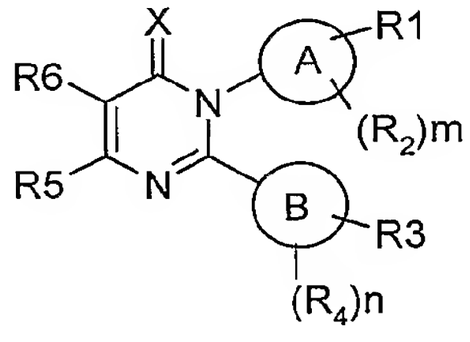
Brief description of the figures

Figures 1 and 2 : Inhibition of cell proliferation in MCF-7 breast cancer cells

Figures 3 and 4 : Inhibition of cell proliferation in MDA-MB-231 breast cancer cells

Claims

1. Novel pyrimidone derivatives of the formula (I)



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein X represents oxygen, sulfur or NR, wherein R represents hydrogen, hydroxyl, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, alkoxyamino group; the rings represented by A and B are selected from aryl or heteroaryl; R^1 represents SR^7, or $S(O)_pR^8$; R^3 represents hydrogen, SR^7, or $S(O)_pR^8$, wherein R^7 represents alkyl or aryl; R^8 represents alkyl, amino or aryl group; and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylslfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; R^5 and R^6 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, aryl, aralkyl, haloalkyl, acyl, alkoxy, aryloxy, aralkoxy, heteroaryl, heterocyclyl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or COR^9, wherein R^9 represents hydroxyl, amino, halogen, alkoxy, aryloxy, monoalkylamino, dialkylamino, arylamino, groups; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2.

2. Novel pyrimidone derivatives of the formula (I) as claimed in claim 1, wherein the ring systems represented by A and B are selected from phenyl, naphthyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl or indolyl.

3. Novel pyrimidone derivatives of the formula (I) as claimed in claim 1, which are selected from :

5-Cyano-4-methylthio-1-(4-methylthio-phenyl)-2-phenyl-1,6-dihydro-pyrimidin-6-one;

5-Cyano-4-methylthio-1-(4-methylthio-phenyl)-2-(4-trifluoromethylphenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-fluorophenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-2-(4-methylsulfonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-fluorophenyl)-2-(4-methylsulfonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylsulfonyl-2-(4-methylsulfonyl-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylsulfonyl-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylthio-2-(4-sulfamoyl-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-fluorophenyl)-1-(4-methylthio-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-fluorophenyl)-1-(4-methylsulfonyl-phenyl)-4-methylthio-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-fluorophenyl)-4-methylthio-1-(4-sulfamoyl-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-2-(4-chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

5-Cyano-1-(4-methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;

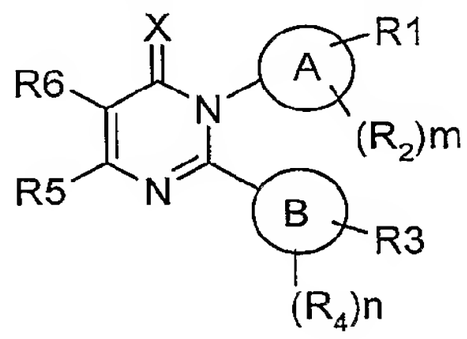
2-(4-Methanesulfonyl-phenyl)-4-methylsulfanyl-6-oxo-1-(4-methylphenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid;

2-(4-Methanesulfanyl-phenyl)-4-methylsulfanyl-6-oxo-1-(4-methylphenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid;

2-(4-Fluroro-phenyl)-4-methylsulfanyl-6-oxo-1-(4-methylphenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid;

5-Carboxy-4-methylthio-1-(4-methylthio-phenyl)-2-phenyl-1,6-dihydro-pyrimidin-6-one;
5-Carbamoyl-2-(4-fluorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;
5-Chloro-2-(4-chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;
2-(4-Chlorophenyl)-4-methylthio-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;
2-(4-Chlorophenyl)-1-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;
1-(4-Methylphenyl)-4-methylthio-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;
1-(4-Methylphenyl)-2-(4-methylthio-phenyl)-1,6-dihydro-pyrimidin-6-one;
4-(5-Cyano-4-methylthio-6-oxo-2-phenyl-6H-pyrimidin-1-yl)-benzenesulfonamide;
4-(5-Cyano-4-methylthio-6-oxo-2-(4-methylphenyl)-6H-pyrimidin-1-yl)-benzenesulfonamide and
4-(5-Carboxy-4-methylthio-6-oxo-2-phenyl-6H-pyrimidin-1-yl)-benzenesulfonamide.

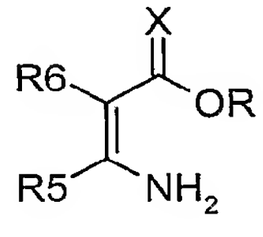
4. A process for the preparation of novel pyrimidone derivatives of the formula (I)



(I)

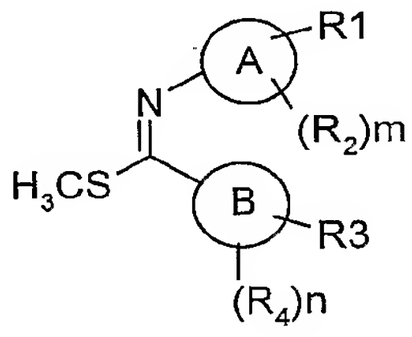
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein X represents oxygen, sulfur or NR, wherein R represents hydrogen, hydroxyl, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, alkoxyamino group; the rings represented by A and B are selected from aryl or heteroaryl; R^1 represents SR^7, or $S(O)_pR^8$; R^3 represents hydrogen, SR^7, or $S(O)_pR^8$, wherein R^7 represents alkyl or aryl; R^8 represents alkyl, amino or aryl group; and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylslfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; R^5 and R^6 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, aryl, aralkyl, haloalkyl, acyl, alkoxy, aryloxy, aralkoxy, heteroaryl, heterocyclyl, monoalkylamino, dialkylamino, acylamino,

alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or COR^9, wherein R^9 represents hydroxyl, amino, halogen, alkoxy, aryloxy, monoalkylamino, dialkylamino, arylamino, groups; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2, which comprises reacting a compound of the formula (Ia)



(Ia)

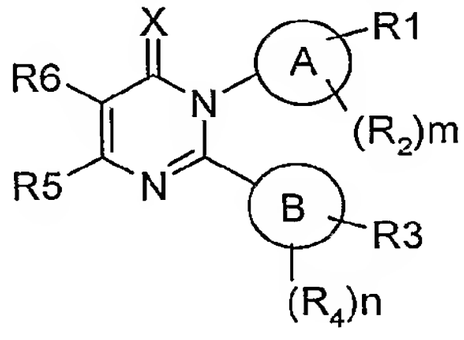
where R represent (C_1-C_3) alkyl group, X, R^5 and R^6 are as defined above, with a compound of the formula (Ib)



(Ib)

wherein all symbols are as defined above, to produce a compound of formula (I) using appropriate solvents under acidic conditions.

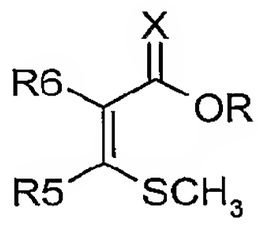
5. A process for the preparation of novel pyrimidone derivatives of the formula (I)



(I)

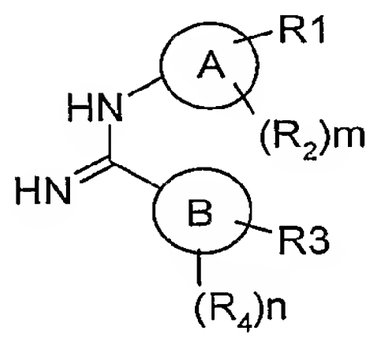
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein X represents oxygen, sulfur or NR, wherein R represents hydrogen, hydroxyl, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, alkoxyamino group; the rings represented by A and B are selected from aryl or heteroaryl; R^1 represents SR^7, or $S(O)_pR^8$; R^3 represents hydrogen, SR^7, or $S(O)_pR^8$, wherein R^7 represents alkyl or aryl; R^8 represents alkyl, amino or aryl group; and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylslfanyl,

sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; R^5 and R^6 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, aryl, aralkyl, haloalkyl, acyl, alkoxy, aryloxy, aralkoxy, heteroaryl, heterocyclyl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or COR^9, wherein R^9 represents hydroxyl, amino, halogen, alkoxy, aryloxy, monoalkylamino, dialkylamino, arylamino, groups; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2, which comprises reacting a compound of the formula (Ic)



(Ic)

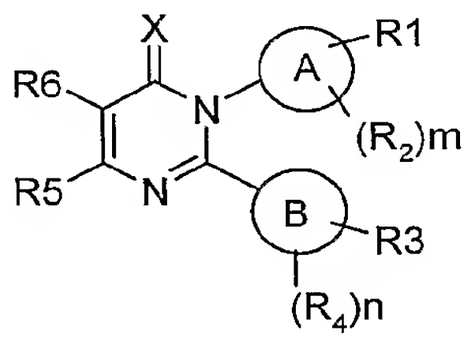
where R represent (C_1-C_3) alkyl group and all other symbols are as defined above, with a compound of the formula (Id)



(Id)

wherein all symbols are as defined above, to produce a compound of formula (I) using appropriate solvents under acidic conditions.

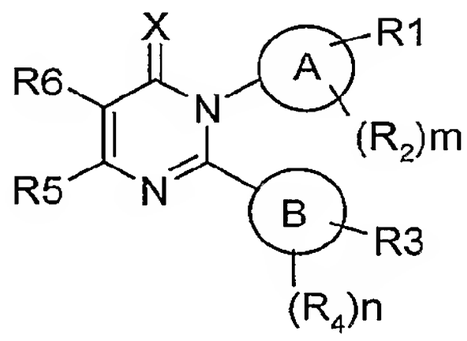
6. A process for the conversion of novel pyrimidone derivatives of the formula (I) as claimed in claim 1,



(I)

wherein any one of the groups R^1 and R^3 represent SR^7, wherein R^7 represents alkyl or aryl and all other symbols are as defined in claim 1, to novel pyrimidone derivatives of the formula (I) wherein any one of the groups R^1 and R^3 represent $S(O)_pR^8$, where p represents 1 or 2 and R^8 represents alkyl or aryl, and all other symbosl are as defined above, using an oxidizing agent.

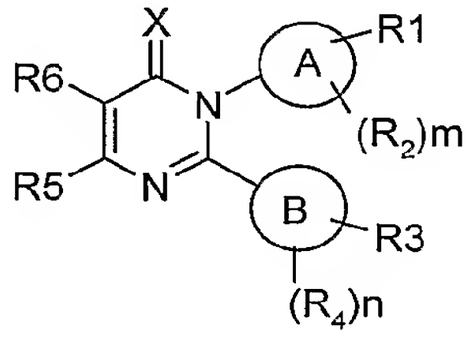
7. A process for the conversion of novel pyrimidone derivatives of the formula (I) as claimed in claim 1,



(I)

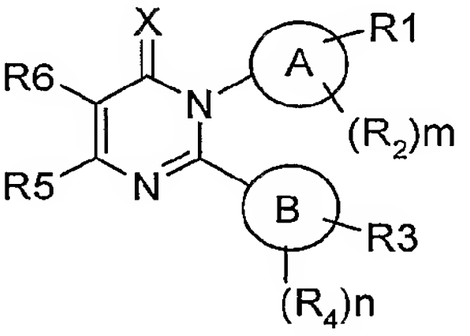
wherein any one of the groups R^1 and R^3 represent $S(O)_pR^8$, where p is 1 or 2, R^8 represents alkyl or aryl and all other symbols are as defined in claim 1, to novel pyrimidone derivatives of the formula (I) wherein any one of the groups R^1 and R^3 represent $S(O)_pR^8$, where p is 1 or 2, R^8 represents amino group and all other symbols are as defined in claim 1.

8. A process for the conversion of novel pyrimidone derivatives of the formula (I) as claimed in claim 1,



(I)

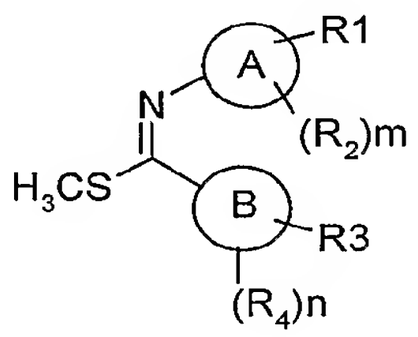
wherein either of the groups R^1 or R^3 represent $S(O)_pR^8$, wherein R^8 represents amino group and p represents an integer of 1 or 2 and all other symbols are as defined in claim 1, which comprises reacting compound of formula (Ie)



(Ie)

wherein R^1 or R^3 represents hydrogen and all other symbols are as defined in claim 1, with chlorosulfonic acid and ammonia.

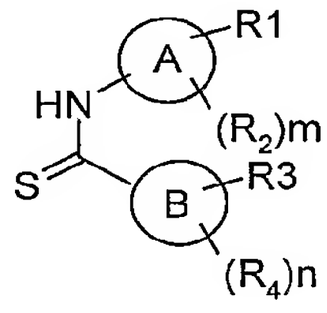
9. A compound of formula (Ib)



(Ib)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein the rings represented by A and B are selected from aryl or heteroaryl; R^1 and R^3 are different and represent hydrogen, SR^7, wherein R^7 represents alkyl or aryl, or $S(O)_pR^8$, wherein R^8 represents alkyl, amino or aryl group and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2.

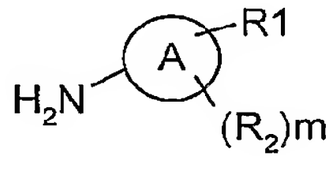
10. A process for the preparation of compound of formula (Ib) as defined in claim 9, which comprises, methylating the compound of formula (Ib-2)



(Ib-2)

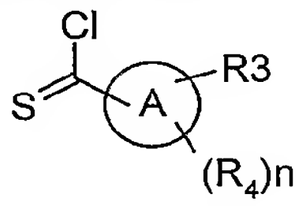
wherein all symbol are as defined in claim 9, using a methylating agent.

11. A process for the preparation of intermediate of formula (Ib-2), which comprises, reacting compound of formula (Ib-3)



(Ib-3)

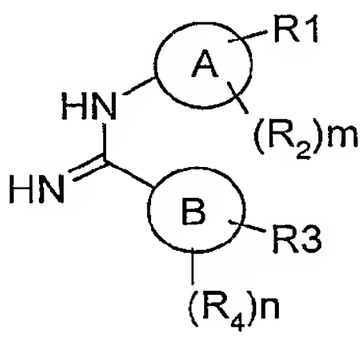
where R_1 and R_2 all are as defined in claim 9 with compound of formula (Ib-4)



(Ib-4)

where all symbols are as defined in claim 9.

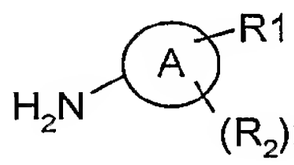
12. A compound of formula (Id)



(Id)

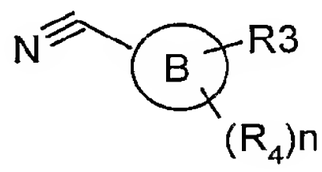
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, and their pharmaceutically acceptable salts, wherein the rings represented by A and B are selected from aryl or heteroaryl; R^1 and R^3 are different and represent hydrogen, SR^7, wherein R^7 represents alkyl or aryl, or $S(O)_pR^8$, wherein R^8 represents alkyl, amino or aryl group and p represents an integer of 1 or 2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; m is an integer and is in the range of 0 to 2; n is an integer and is in the range of 0 to 2..

13. A process for the preparation of compound of formula (Id) as defined in claim 12, which comprises, reacting compound of formula (Ib-3)



(Ib-3)

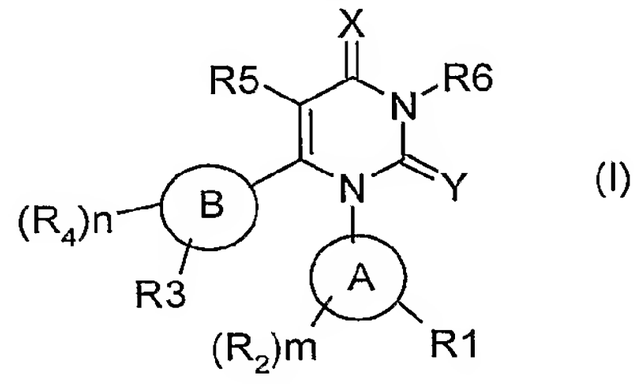
where R_1, R_2 and m are as defined in claim 12, with compound of formula (Id-1)



(Id-1)

where all symbols are as defined in claim 12, in the presence of catalysts and solvent.

14. A pharmaceutical composition which comprises a compound of formula (I)



(I)

as defined in claim 1 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

15. A pharmaceutical composition as claimed in claim 13, in the form of a tablet, capsule, powder, syrup, solution or suspension.

16. A pharmaceutical composition which comprises a compound as claimed in claim 3 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

17. A pharmaceutical composition as claimed in claim 15, in the form of a tablet, capsule, powder, syrup, solution or suspension.

18. Use of a compound of formula (I) as claimed in claim 1, for the prophylaxis or treatment of rheumatoid arthritis; osteophorosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster infection.

19. Use of a compound as claimed in claim 3, for the prophylaxis or treatment of rheumatoid arthritis; osteophorosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster infection.

20. Use of a composition as claimed in claim 14, for the prophylaxis or treatment of rheumatoid arthritis, Pagets disease, osteophorosis, multiple myeloma, uveititis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection.

21. Use of a compound of formula (I) as claimed in claim 1 for lowering plasma concentrations of either or both TNF-α and IL-1.

22. Use of a compound as claimed in claim 3 for lowering plasma concentrations of either or both TNF-α and IL-1.

23. Use of a composition as claimed in claim 14 for lowering plasma concentrations of either or both TNF-α and IL-1.

24. Use of a compound of formula (I) as claimed in claim 1 for lowering plasma concentrations of either or both IL-6 and IL-8.

25. Use of a compound as claimed in claim 3 for lowering plasma concentrations of either or both IL-6 and IL-8.

26. Use of a composition as claimed in claim 14 for lowering plasma concentrations of either or both IL-6 and IL-8.

27. Use of a compound of formula (I) as claimed in claim 1 for the prophylaxis or treatment of a pain disorder.

28. Use of a compound as claimed in claim 3 for the prophylaxis or treatment of a pain disorder.

29. Use of a composition as claimed in claim 14 for the prophylaxis or treatment of a pain disorder.

30. Use of a compound of formula (I) as claimed in claim 1 for decreasing prostaglandin production.

31. Use of a compound as claimed in claim 3 for decreasing prostaglandin production.

32. Use of a composition as claimed in claim 14 for decreasing prostaglandin production.

33. Use of a compound of formula (I) as claimed in claim 1 for decreasing cyclooxygenase enzyme activity.

34. Use of a compound according to claim 34, wherein the cyclooxygenase enzyme is COX-2 or COX-3.

35. Use of a compound as claimed in claim 3 for decreasing cyclooxygenase enzyme activity.

36. Use of a compound according to claim 35, wherein the cyclooxygenase enzyme is COX-2 or COX-3.

Figure 1

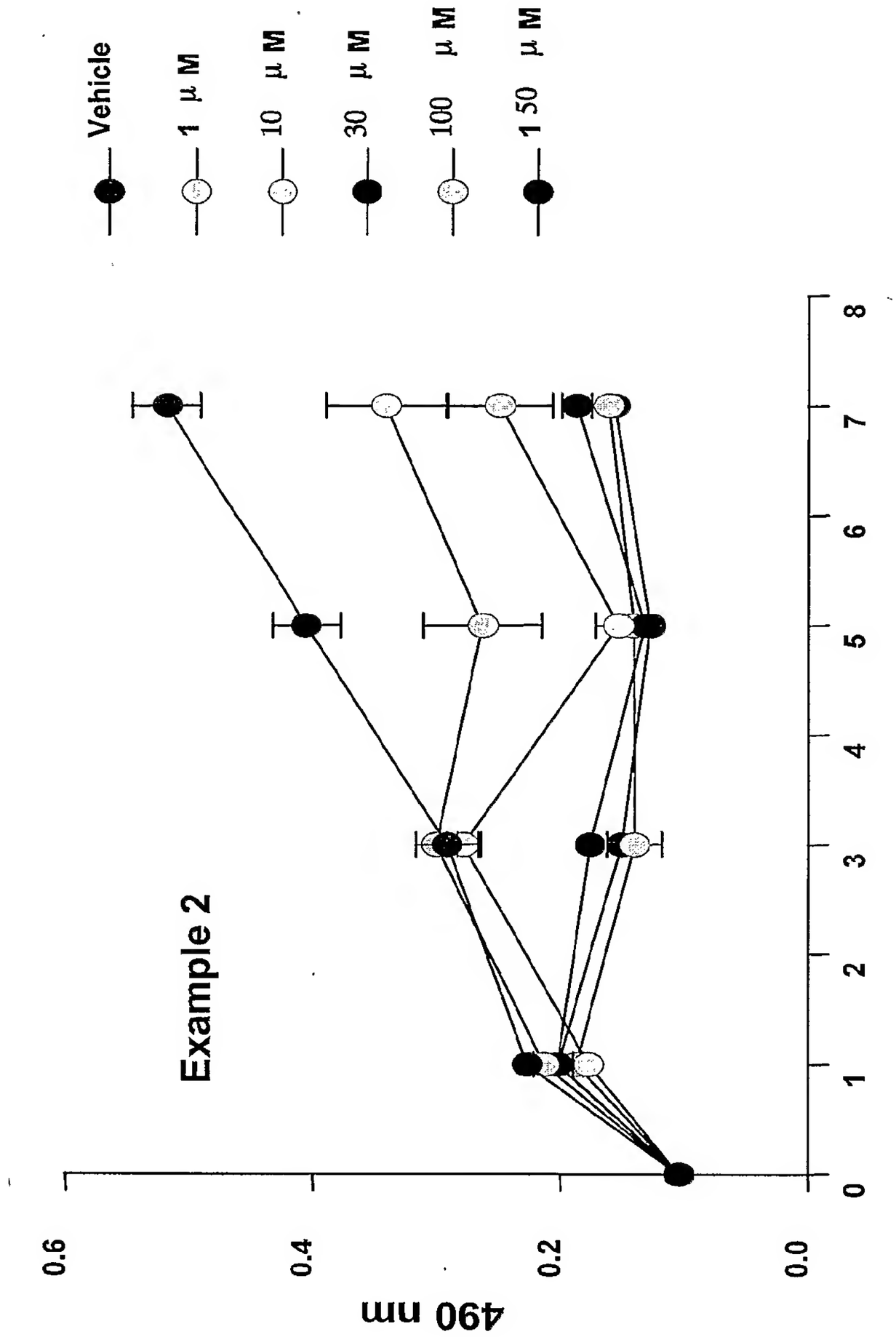

Vehicle
1 µM
10 µM
30 µM
100 µM
150 µM
Example 2
490 nm
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
8
Treatment, Days

Figure 2

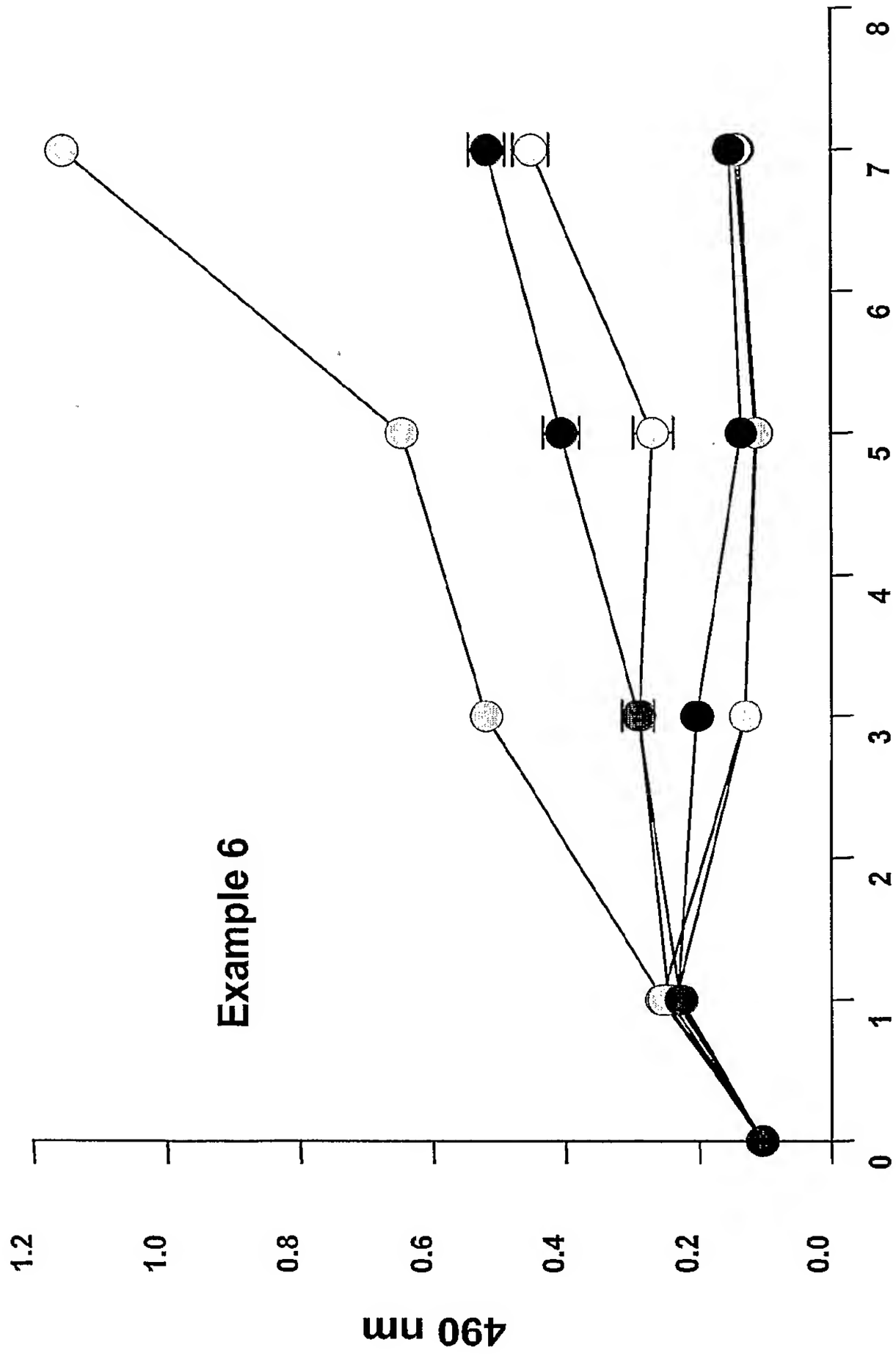


Figure 3

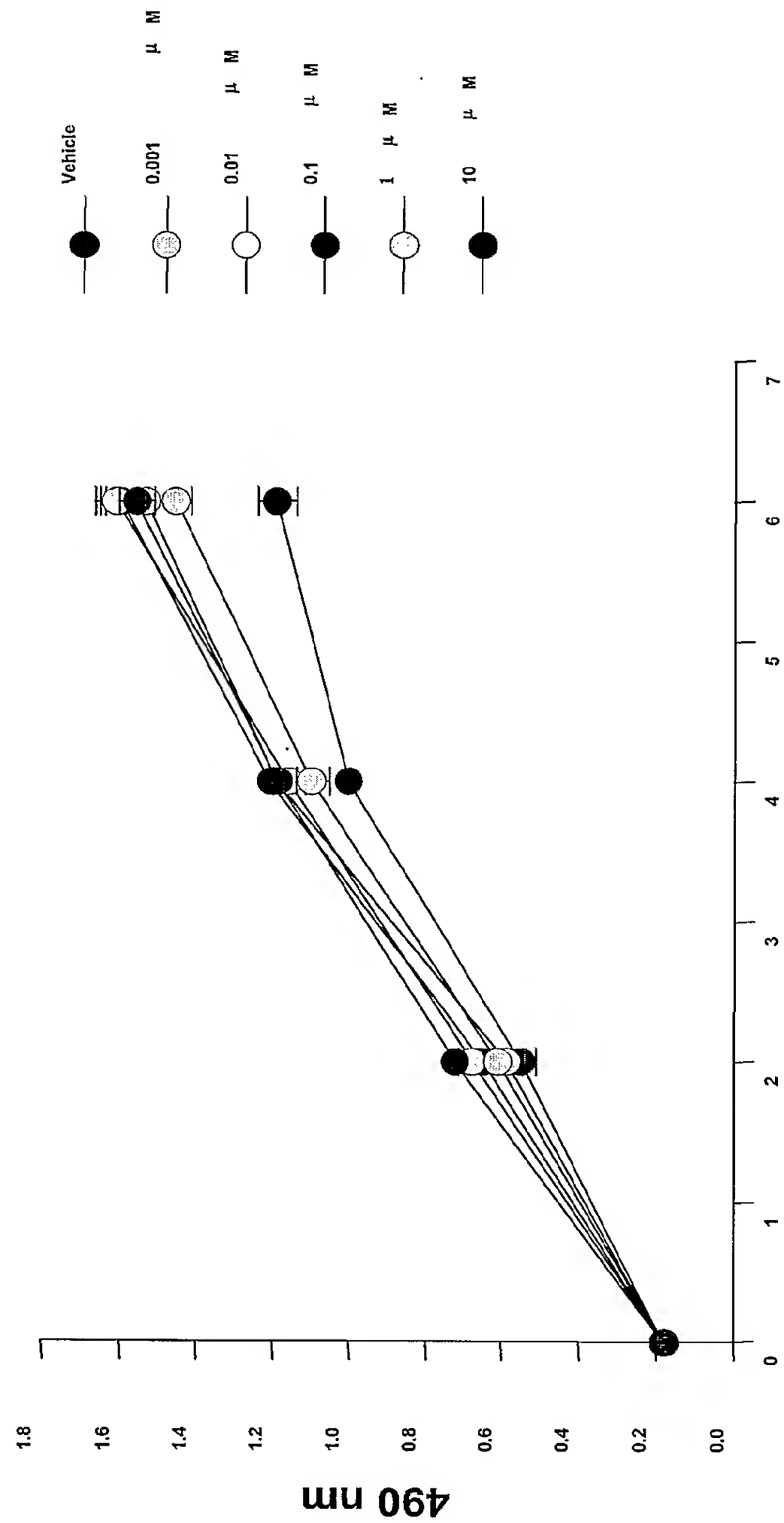
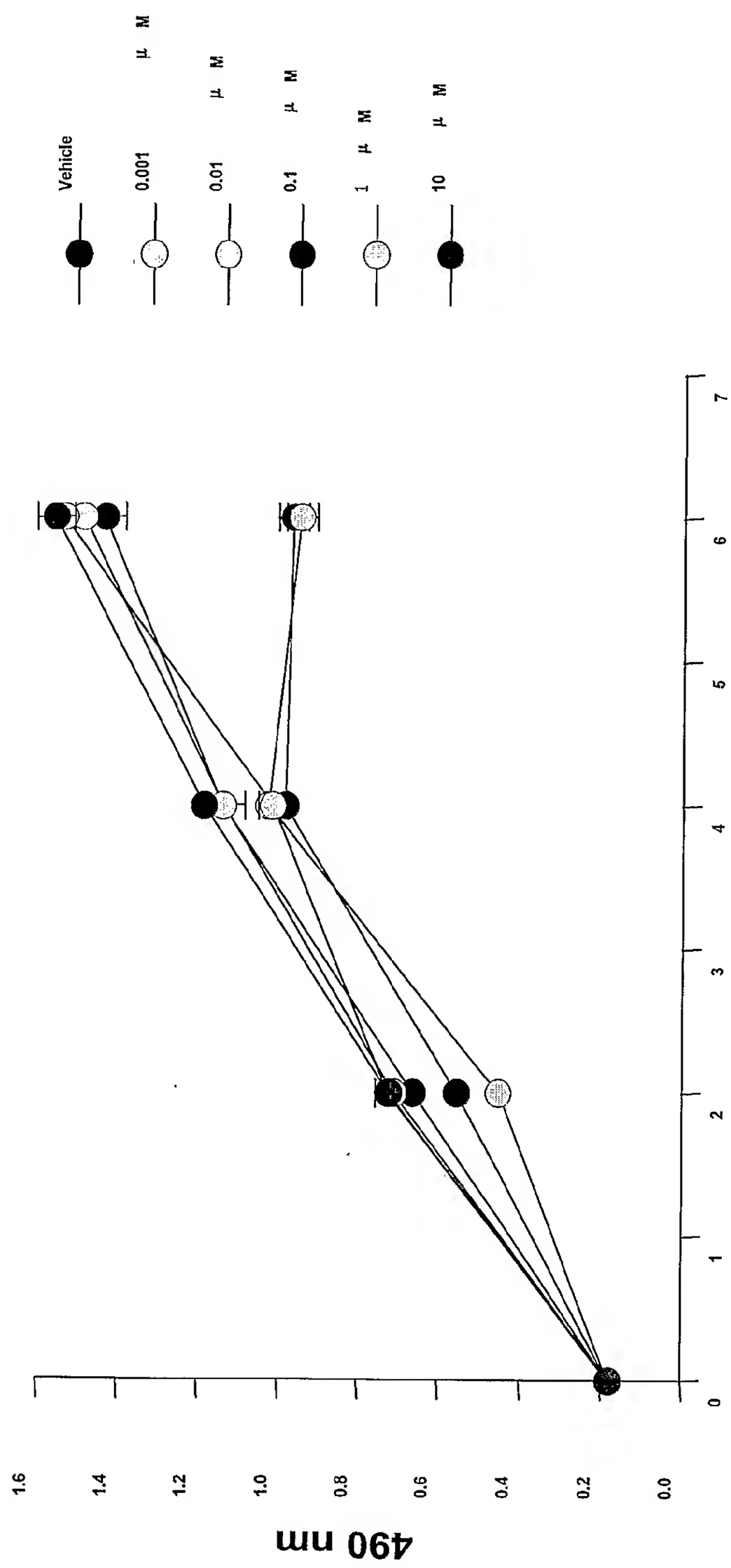

Example 2
490 nm
Treatment, Days
Vehicle
0.001 μM
0.01 μM
0.1 μM
1 μM
10 μM
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
0
1
2
3
4
5
6
7

Figure 4


Vehicle
0.001 μM
0.01 μM
0.1 μM
1 μM
10 μM
Example 6
490 nm
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
Treatment, Days